REMARKS

Claims 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60-68, 71 and 87-104 constitute the pending claims in the present application. Applicants cancel, without prejudice, claim 62. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants apologize for the inadvertent mis-numbering of claims in the preliminary amendment filed December 31, 2001. Applicants have corrected the numbering of the claims and believe that the numbering is in accordance with 37 CFR 1.126.

2. Applicants note that claims 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60-68, 71 and 87-104 are pending in the instant application. Claims 1-10, 15, 25, 27-31, 34, 39, 40, 46, 49, 50, 53, 56, 57, 66-68 and 71 have been amended, claims 11-13, 16-18, 20, 21, 32, 33, 36-38, 43-45, 51, 52, 54, 55, 58, 59, 69, 70, and 72-86 have been canceled, and claims 87-104 have been added.

3. Applicants maintain the arguments of record with regard to the restriction requirement. Nevertheless, Applicants acknowledge that claims 19, 22-27, 34, 35, 39, 47, 49, 60, 61 and 90-92 are withdrawn from consideration as being directed to a non-elected invention. Applicants will cancel non-elected claims upon indication of allowable subject matter. Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are currently under examination.

4. Applicants enclose herewith an Information Disclosure Statement for the Examiner's consideration.

5. Applicants have amended the specification to provide the necessary reference to the prior applications.

6. Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 3, 6, 10-18, 41-46, 48, 74, 77-79, 85 and 94-97 of copending Application No. 09/325,256. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

7. Applicants' amendment to the specification is believed to obviate the objection.

8. Claim 62 is objected to under 37 CFR 1.75 as being a duplicate of claim 5. Cancellation of claim 62 is believed to obviate the objection.

9.1 Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse this rejection.

The Office Action agrees that Applicants have provided a number of working examples which demonstrate that hedgehog proteins can be modified with any of a variety of different hydrophobic moieties using the methods of the invention to increase the potency and stability of the protein. The Office Action also agrees that the specification provides a list of other extracellular signaling proteins which may be modified using the methods of the present invention. However, the basis of the current rejection appears to be that the making and testing of other proteins modified using the methods of the present invention would involve undue experimentation. It is with this contention which Applicants vehemently disagree.

The MPEP provides specific guidance in evaluating whether the level of experimentation required is undue. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (MPEP 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (International Trade Commission 1983); *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404). The factors to be weighed when evaluating undue experimentation (the so-called Wands Factors) include the state of the prior art, the level of skill in the art, the amount of guidance provided by the specification, and the existence of working examples.

In the context of the present application, the state of the art and the level of skill in the art is high. Basic techniques in molecular biology and chemistry are well known in the art, and allow one of skill to readily make and purify recombinant proteins for use in the subject invention. However, the present application does not simply rely on the high level of skill in the

art, but also provides extensive guidance. For example, the making of recombinant polypeptides, as well as variant polypeptides modified to contain a mutation, linker, or sequence to facilitate purification, is reviewed in detail (page 22, line 22 – page 31, line 21).

In terms of working examples, the Examiner appears to agree that the present application certainly provides working examples which indicate that the invention works as Applicants allege. Applicants show that modification of human sonic hedgehog, rat sonic hedgehog, and Indian hedgehog enhances at least one physio-chemical property of the protein. Furthermore, Applicants provide evidence for the making and testing of a variety of different hydrophobic modifications including cholesterol, palmitoyl, myristoyl, and stearol, as well as modifications using several different methods such as acylation via a fatty acid-thioester donor. Accordingly, Applicants contend that the application provides a number of working examples which support the enablement of the full scope of the claims.

Finally, an important criteria for evaluating undue experimentation is the amount of guidance provided by the specification. As outlined above, both the MPEP and the Courts have asserted that the need for experimentation does not undermine the enablement of the claimed invention, as long as the experimentation is not undue. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224,195 USPQ, 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2s 1400, 1404 (Fed. Cir. 1988).

The present application has provided extensive guidance to one of skill in the art. For example, the making of recombinant polypeptides and variant polypeptides is reviewed on page 22, line 22 – page 31, line 21. Following this review of basic techniques in molecular biology and combinatorial mutagenesis, which are routinely used in the art to make and purify polypeptides and variants, the specification provides detailed guidance as to the making of polypeptide derivatives. The making of hydrophobic derivatives is reviewed on page 31, line 23 – page 41, line 7. The making of polypeptides derivatized with a hydrophobic peptide is

reviewed on page 41, line 9 – page 42, line 7. The making of lipid derivatives is reviewed on page 42, line 9 – to page 45, line 30. Given the high level of skill in the art, and the extensive guidance provided by the specification, one of skill in the art would readily be able to make the claimed polypeptides using the presently claimed methods of the present invention.

Finally, the specification provides extensive guidance as to methods of testing the polypeptides of the present invention to confirm that they meet the limitations of the claims (e.g., improved bioactivity, binds to a receptor with substantially the same affinity, etc.). Working examples of such commonly used methods are shown for hedgehog polypeptides modified using the methods of the present invention. For example, the activity of a modified protein can be tested in a cell-based assay which is known to correlate with the activity of the protein. In the case of hedgehog, C3H10T1/2 cells are such a cell-based assay (Example 3, page 61, lines 1-23). The choice of the appropriate cell-based assay based on the particular polypeptide modified by the methods of the present invention can be readily made by one of skill in the art. In addition to such cell-based activity assays, binding affinity of the modified polypeptide for its receptor or coreceptor can be readily determined using either cell-based or cell-free binding affinity assays (page 61, lines 24-29). Accordingly, Applicants contend that the specification has provided extensive guidance such that one of skill in the art can readily test the polypeptides modified by the methods of the present invention to select the polypeptides which have the desired activity.

Applicants' disclosure satisfies all of the requirements under 35 U.S.C. 112, first paragraph. As discussed in detail above, the specification provides extensive guidance such that one of skill in the art can readily test the polypeptides modified by the methods of the present invention and select the polypeptides which have the desired activity. This is the standard clearly delineated in the MPEP which additionally points out that "the presence of inoperative embodiments within the scope of a claims does not necessarily render a claim nonenabled." MPEP 2164.08 (b).

Given the high level of skill in the art, the presence of multiple working examples of the presently claimed methods and compositions, and the extensive guidance regarding the making and testing of polypeptides modified by the methods of the present invention, Applicants contend that the modified polypeptides of the invention, and the methods of making such modified

polypeptides are enabled throughout their scope. Applicants respectfully request reconsideration and withdrawal of the rejection.

Additionally, however, Applicants point out that the claims currently under consideration include both claims directed to compositions of modified polypeptides and claims directed to the methods of making modified polypeptides. Applicants submit that the consideration of Applicants' arguments and the determination of the enablement of the presently claimed invention should be evaluated separately for claims directed to the compositions (claims 1-10, 14, 15, 28-31, 48, 66, 67 and 93-104) and for claims directed to the methods (40-42, 46, 50, 53, 56, 57, 63-65, 68, 71, 87-89).

9.2 Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection.

Firstly, as outlined above, Applicants submit that the evaluation of whether the claims satisfy the requirements under 35 U.S.C. 112, first paragraph, must be separately undertaken for claims directed to the composition (claims 1-10, 14, 15, 28-31, 48, 66, 67 and 93-104) and for claims directed to the methods (40-42, 46, 50, 53, 56, 57, 63-65, 68, 71, 87-89). In fact, Applicants respectfully point out that the explanation provided in the prior Office Action for the written description rejection appears to be entirely directed to whether the specification provides adequate written description for the compositions of modified polypeptides, and not to whether the specification provides adequate written description of the methods for making modified polypeptides.

For the sake of completeness in responding to this rejection, Applicants point out that the specification provides extensive description of methods for making modified polypeptides. The specification readily allows one of skill in the art to envision the process required to modify a given polypeptide. Furthermore, as outlined in detail above, Applicants provide extensive teachings as to methods of testing modified polypeptides. Such teachings allow one to readily envision the testing of polypeptides modified by the presently claimed methods in order to

identify those which possess the desired activity. Accordingly, Applicants contend that claims directed to methods of modifying polypeptides (40-42, 46, 50, 53, 56, 57, 63-65, 68, 71, 87-89) are adequately described in the specification. If the Examiner believes that claims directed to the methods do not satisfy the requirements under 35 U.S.C. 112, first paragraph, Applicants respectfully request clarification as to the basis of this rejection. Reconsideration and withdrawal of this rejection is requested.

The Office Action alleges that although Applicants have provided an adequate written description of the genus of hedgehog polypeptides, Applicants have failed to provide an adequate written description of the genus of modified polypeptides which meet the limitations of the pending claims. Accordingly, the Office Action alleges that one of skill in the art cannot readily envision the presently claimed compositions. Applicants respectfully disagree with the analysis provided in the last Office Action. Although the last Office Action cites the *Regents of the University of California v Eli Lilly & Co* to support the basis of this rejection, Applicants contend that the analysis applied in the Office Action is inconsistent with the finding of the Court in that case. The standard for assessing compliance with the written description requirement has been outlined in detail by the Guidelines for the Examination of Patent Applications which indicate that possession of the invention can be demonstrated in many ways including "by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."

This assertion is supported by the Federal Circuit's finding in *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1997 U.S. App. LEXIS 18221, 43 U.S.P.Q.2D (BNA) 1398 (Fed. Cir. 1997). The Federal Circuit addressed the question of how to adequately describe a genus of materials. In outlining that which constitutes an adequate description of a genus with respect to genetic material, the court asserted that adequate description requires more than the gene or protein name.

> "[A] cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the DNA. See Fiers, 984 F.2d at 1171, 25 U.S.P.Q.2D (BNA) at 1606. A description of a genus of cDNAs may be achieved by means of a recitation of a representative

> number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."** (emphasis supplied) 119 F.3d at 1566

Accordingly, for the description of a genetic invention to be deemed adequate to describe the genus that the claims encompass requires either a recitation of the structure of a representative number of members of the genus **or** a recitation of the common features of the members of the claimed genus. This "recitation of structural features common to the members of the genus" is analogous to the way in which chemical genera are described, and provides features which readily allow one of skill in the art to recognize the claimed invention. This is in contrast to the way in which the claimed subject matter was recited in Lilly, where nucleic acids were claimed by the name of the cDNA and its origin, without any recitation of sequence or common structural or functional characteristics that could be used by one of skill in the art to readily envision the claimed sequences.

> "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." 119 F.3d at 1566

Applicants submit that the pending claims define the claimed subject matter in terms of generic formulae that indicate with specificity what the generic claims encompass, and accordingly meet the guidelines set forth above and comply with the written description requirement. Applicants have disclosed structural features (e.g., specification hydrophobic modification appended to specific portions of a polypeptide) which readily allow one of skill in the art to envision the presently claimed subject matter. The specification provides extensive discussion of the making and testing of modified polypeptides, and further provides working

examples to demonstrate that the structural features adequately describe modified polypeptides which meet the limitations of the claims.

In addition to the extensive structural limitations provided in the claims which allow one of skill in the art to readily envision that which is being claimed, Applicants describe functional attributes which the claimed modified polypeptides possess. In short, Applicants describe the claimed polypeptides both structurally and functionally. Such structural and functional description of the claimed invention allows one of skill in the art to readily envision Applicants' invention, and stands in sharp contrast to the way in which compositions were described in *Lilly*. Accordingly, Applicants submit that based on both the Guidelines for the Examination of Patent Applications, and based on the findings of the Federal Circuit, Applicants have satisfied the requirements under 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

10. Claims 1-10, 14, 15, 62, 68, 87-89 and 93-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims. Reconsideration and withdrawal of the rejection is respectfully requested.

(a) Claims 1-10, 14, 15 and 62 are rejected for allegedly lacking clarity in the recitation of "wherein the protein...". To improve the clarity of the claims, Applicants have amended the claims to incorporate the Examiner's suggestions. Applicants' amendments are not in acquiescence of the rejection, and are solely to expedite prosecution of the present application. Applicants contend that the amendments are made solely for clarity and do not narrow the scope of the claims.

(b) Claims 87 and 88 are rejected because the phrase "the hydrophobic moiety" allegedly lacks proper antecedent basis. Applicants' amendment to claim 87 to supply proper antecedent basis is believed to obviate the rejection. Applicants' amendment was made solely to clarify the language of the claim and is not believed to narrow the scope of the claim.

(c) Claims 68, 87-89 and 93-104 are rejected over the recitation of "the extracellular receptor". To expedite prosecution, Applicants have amended the claims to more explicitly point out the claimed subject matter. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

11. Claims 1, 3-5, 10, 93, 95-97 and 102 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Jonassen et al., WO 96/29342. Applicants traverse this rejection.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). "The identical invention must be shown in as complete detail as is contained in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicants contend that Jonassen et al. fails to satisfy this criteria for anticipating the present invention. Jonassen et al. teach lipophilic modification of small peptide hormones. Jonassen et al. further provide one example where the lipophilic modification of a small peptide hormone increases the protraction of the modified hormone at a site of injection. Clearly, however, Jonassen et al. fail to teach or suggest each and every limitation of the present claims. The present claims are directed to modification of isolated proteins. Jonassen et al. only provides for the modification of small peptide hormones, and this reference neither teaches nor suggests that proteins can be modified to achieve any desirable effect. Even if one would have been motivated to apply the teachings of Jonassen et al. to the modification of large proteins, Jonassen et al. provides only an invitation to one of skill in the art to attempt such work. Jonassen et al. alone does not provide a reasonable expectation of success that large proteins, such as hedgehog polypeptides, can be modified with hydrophobic moieties to achieve desirable properties, since the relative size of small peptide hormones makes it easier to manipulate their physico-chemical properties by attachment of such moieties.

Additionally, the present claims further require that hydrophobic modification of the protein does not substantially alter the binding affinity of the protein to its receptor or coreceptor.

The teachings of Jonassen et al. are completely silent on this issue. One of skill in the art has no way of knowing whether the modified peptides of Jonassen et al. bind to their cognate receptors at all, whether they bind with some altered affinity, or whether they bind with the same affinity. However, MPEP 2112 clearly points out that "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."

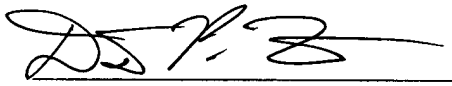
> "In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities** (emphasis added). The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed Cir. 1999) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fasterning element, either expressly or inherently.)" **MPEP 2112**

Accordingly, Applicants respectfully submit that Jonassen et al. fail to meet the limitations of the present claims and thus fail to anticipate the claimed subject matter. Reconsideration and withdrawal of this rejection are requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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